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Murine double minute 2, a potential p53-independent regulator of liver cancer metastasis

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Abstract

Hepatocellular carcinoma (HCC) has emerged as one of the most commonly diagnosed forms of human cancer; yet, the mechanisms underlying HCC progression remain unclear. Unlike other cancers, systematic chemotherapy is not effective for HCC patients, while surgical resection and liver transplantation are the most viable treatment options. Thus, identifying factors or pathways that suppress HCC progression would be crucial for advancing treatment strategies for HCC. The murine double minute 2 (MDM2)-p53 pathway is impaired in most of the cancer types, including HCC, and MDM2 is overexpressed in approximately 30% of HCC. Overexpression of MDM2 is reported to be well correlated with metastasis, drug resistance, and poor prognosis of multiple cancer types, including HCC. Importantly, these correlations are observed even when p53 is mutated. Indeed, p53-independent functions of overexpressed MDM2 in cancer progression have been suitably demonstrated. In this review article, we summarize potential effectors of MDM2 that promote or suppress cancer metastasis and discuss the p53-independent roles of MDM2 in liver cancer metastasis from clinical as well as biological perspectives.

Keywords

Murine double minute 2; metastasis; effectors; hepatocellular carcinoma; p53 independent

INTRODUCTION

Liver cancer is the 5th most frequently diagnosed cancer worldwide in males (9th in females) and is the 2nd leading cause of cancer-related death in males (6th in females).[1] Around 80% of hepatocellular carcinoma (HCC) cases occur in developing countries, mainly due to the incidence of hepatitis B and hepatitis C infections.[2] HCC is often diagnosed at late stages, and the 5-year survival rate for metastatic HCC is less than 10% (http://www.cancer.org/acs/groups/cid/documents/webcontent/003114-pdf.pdf).[3–5]

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Conflicts of interest

There are no conflicts of interest.

Understanding the mechanisms involved in the regulation of HCC metastasis and discovering methods or compounds to suppress metastasis would be highly beneficial for HCC patients.[6]

Metastasis is a cellular process which involves multiple cascades including detachment of cancer cells from primary tumors, migration, intravasation, survival in the vasculature, extravasation, and colonization at a secondary site.[7] Multiple factors play a role in each metastatic step and the inhibition of any of these steps would be helpful in blocking the cancer spread. Although distant metastasis is not a common event in HCC, HCC often shows vascular invasion, intrahepatic colonization, and lymph node metastasis. This is most likely due to the dense hepatic vasculature which supports the intrahepatic metastasis of HCC.[8]

The murine double minute 2 (MDM2) was originally identified as a gene which was overexpressed in a spontaneously transformed mouse cell line (3T3-DM),[9] and the gene product was found to transform normal cells.[10] The primary function of MDM2 is to ubiquitinate the tumor suppressor p53 for inducing its degradation. Hence, MDM2 overexpression greatly contributes to tumor development through inhibition of p53 activity. MDM2 is also a transcriptional target of p53, hence forming autoregulatory negative feedback loop.[11]

Increasing evidence, however, indicates that MDM2 also has p53-independent functions toward malignant progression when overexpressed. Approximately 10% of human cancers have both MDM2 overexpression and mutant p53.[12] Mice carrying a MDM2 transgene develop a higher percentage of sarcomas regardless of p53 status, as compared with p53-null mice.[13] Ectopic expression of MDM2 in mammary epithelial cells of mice, as well as in mouse embryonic fibroblasts (MEFs), increases aneuploidy and chromosome/chromatid breaks regardless of p53 status.[14,15] MDM2 interacts with different proteins and alters their activities, leading to malignant progression independent of p53.[11] Specifically, MDM2 inhibits Nijmegen breakage syndrome 1, leading to inhibition of double-strand break repair.[16] MDM2 also promotes p21 degradation.[17,18] Additionally, MDM2 promotes cell cycle progression through activation of S-phase, via interaction with the retinoblastoma tumor suppressor protein and the transcriptional factor E2F.[19,20] MDM2 furthermore enhances doxorubicin resistance in acute lymphoblastic leukemia cells through its binding to the Sp1-binding site in the p65 promoter.[21] MDM2 is shown to bind to Sp1 and inhibit Sp1-dependent transcription.[22] Thus, numerous MDM2 binding partners and effectors contribute to its p53-independent functions.[23]

MDM2 overexpression is clinically correlated with metastasis of multiple cancer types including liver cancer,[24–27] but the underlying mechanisms remain unclear. In this review, we focus on p53-independent roles of MDM2 in cancer metastasis, specifically in liver cancer. We categorize effectors of MDM2 into metastasis promoters [Table 1] and suppressors [Table 2].

METASTASIS PROMOTERS

Hypoxia-inducible factor-1-alpha

Hypoxia-inducible factor-1-alpha (HIF-1α) and HIF-1β are a class of transcription factors that play a key role in regulating cellular response against hypoxia.[28] While HIF-1β is constitutively expressed, expression of HIF-1α is dependent on oxygen tension. In normoxic conditions, it is rapidly degraded, whereas in hypoxic states, HIF-1α heterodimerizes with HIF-1β on hypoxia response elements in the promoter regions of numerous downstream target genes, thus promoting tumor invasion, angiogenesis, and metastasis.[29] For example, HIF-1α transactivates Snail1 and vascular endothelial growth factor (VEGF) that accelerate epithelial-mesenchymal transition (EMT), a crucial biologic process for epithelial tumors to gain metastatic potential, and angiogenesis, respectively, thereby enhancing invasion and metastasis.[30] HIF-1α is overexpressed in multiple types of human cancer including HCC.[31,32] Overexpression of HIF-1α is correlated with vascular invasion and poor survival in human HCC.[32–35]

MDM2 directly binds to HIF-1α, and overexpression of MDM2 results in accumulation of HIF-1α in hypoxic cells and increase in hypoxia-induced VEGF transcription.[36,37] Conversely, MDM2 is shown to degrade HIF-1α under hypoxic conditions, which is inhibited by phosphorylation of MDM2 at serine 166 by AKT.[38,39] Thus, the roles of MDM2 in regulating HIF-1α function need to be further investigated. Although both MDM2 and HIF-1α play roles in HCC progression, there is no existing study that directly shows MDM2 enhancing liver cancer metastasis through upregulation of HIF-1α.

Slug

Slug (also known as Snail family zinc finger 2: Snail2) is a member of the Snail family of transcription factors that induce EMT crucial for embryogenesis and cancer metastasis by repressing E-cadherin.[40] Slug is upregulated in many cancer types, including HCC, and its overexpression is associated with invasion and metastasis of HCC.[41–43]

MDM2 is shown to stabilize Slug mRNA in a p53-independent manner, while knockdown of Slug nullifies invasion of HCT116 p53-null colon cancer cells induced by MDM2 overexpression.[44] However, direct evidence demonstrating that MDM2's involvement in promoting HCC metastasis via upregulation of Slug has not yet been demonstrated.

Matrix metalloproteinase-9

Matrix metalloproteinase 9 (MMP-9), is a type IV collagenase whichisagroupofzinc-containingendopeptidasestodegrade structural proteins of extracellular matrix, thus playing a pivotal role in the metastatic process.[45] Overexpression of MMP-9 is well correlated with invasion, metastasis, and poor prognosis in liver cancer.[46–49] Correlation between the expression of MMP-9 and MDM2 is shown in benzopyrene-induced lung cancer in rats, where both protein expression is higher in stage III and IV lung cancer tissues as compared with stage I and II tissues.[50] Also, in human breast cancer, MDM2 expression is positively correlated with that of MMP-9, and is also negatively correlated with disease-free survival.[51] Moreover, knockdown of MDM2 in pancreatic carcinoma SW1990HM cells

results in reduced MMP-9 protein expression,[52] and MDM2 promotes invasion of both MCF7 and MDA-MB-231 cell lines by increasing the MMP-9 promoter activity.[51] Although there is definite clinical and functional correlation between MMP-9 and MDM2, it remains unclear whether MDM2 induces invasion and metastasis in liver cancer through upregulation of MMP-9.

Hu antigen R

Hu antigen R (HuR, also known as ELAV-like protein 1) was first identified in drosophila as a member of the embryonic lethal abnormal vision (ELAV) family RNA-binding proteins.[53,54] HuR binds to AU-rich elements in the 3′ untranslated region of target mRNAs and stabilizes them, resulting in regulation of cell proliferation, survival, immune response, and differentiation.[55] Elevated expression of HuR is reported in many types of cancer.[56,57] Specifically, HuR is upregulated in HCC, and its expression is positively correlated with advanced stages of HCC, as well as poor outcomes in HCC patients.[58] HuR promotes proliferation and differentiation of hepatocytes, as well as HCC transformation.[59] Importantly, MDM2 neddylates HuR, protects it from degradation, and induces its nuclear localization in mouse liver progenitor, colon cancer, and HCC cell lines.[60] Although all the cell lines contain wild-type p53, neddylation of HuR by MDM2 is likely to be p53-independent, which needs to be clarified in the future. Importantly, it also remains unknown whether neddylated HuR by MDM2 enhances HCC metastasis.

METASTASIS SUPPRESSORS

E-cadherin

E-cadherin is a single transmembrane glycoprotein involved in Ca^{2+}-mediated cell adhesion, mobility, and proliferation of epithelial cells and functions as a metastasis suppressor.[61,62] Reduced expression of E-cadherin is correlated with high potential of invasion and metastasis, as well as poor prognosis, in many cancer types including breast,[63] gastric,[64] lung,[65] colorectal,[66] and pancreatic cancer.[67] Also in HCC, reduced E-cadherin expression is associated with high tumor grade, vascular invasion, intrahepatic metastasis, disease progression, and poor outcomes.[68–71]

MDM2 is found to directly interact with E-cadherin and facilitate its degradation in a p53-independent manner.[72] Expression of MDM2 and E-cadherin is inversely correlated in breast cancer having lymph node metastasis.[72] However, it remains unclear whether or not MDM2 promotes HCC metastasis by degrading E-cadherin.

Non-metastatic cells 2

Non-metastatic cells 2 (NME2, also known as NDPK-B, NM23B, NM23-H2) belongs to the nonmetastatic family and functions as a metastasis suppressor.[73] Reduced NME2 expression is associated with increased metastatic potential of oral squamous cell carcinoma, lung, ovarian, colon, and breast cancer.[74–76] However, NME2 expression is found to be increased in HCC.[77,78]

MDM2 interacts with NME2 in H1299 lung cancer and HEK293 embryonic kidney cell lines and also suppresses the ability of NME2 to negatively regulate cell motility in renal cell carcinoma (UOK117 and its derivative 1.27) and H1299 cell lines.[79] However, the role of NME2 in metastasis suppression of HCC and its functional association with MDM2 in HCC remain to be investigated.

TAp63

TAp63, along with TAp73, are tumor suppressor proteins that belong to the p53 family with high homology in the DNA binding domain and recognize the same p53 responsive elements.[80] TAp63 suppresses migration and metastasis in many human cancer types including liver cancer, thus functioning as a metastasis suppressor.[81–86] On the other hand, isoforms of p63 lacking *N*-terminal domain show oncogenic function and are overexpressed in multiple cancer types.[85,87,88] Mice with deletion of the p63 gene spontaneously develop tumors, while compound knockout mice for p53 and p63 show high frequency of metastasis as compared with p53 or p63 knockout mice.[89,90]

TAp63 weakly binds to MDM2,[91] and MDM2 is shown to attenuate apoptotic function of TAp63 by inhibiting its nuclear localization.[92] However, it is unknown whether or not MDM2 inhibits metastasis suppressor function of TAp63. Conversely, it is also reported that MDM2 competes with TAp63 for binding to $p53^{R175H}$ mutant to restore p63 activity,[93] and overexpression of MDM2 increases the steady-state level of intracellular TAp63 and enhances its transcriptional activity.[94] Thus, the functional relationship of MDM2 with TAp63 is controversial.

Forkhead box O family

Forkhead box O (FOXO) proteins (FOXO1, 3, 4, and 6) are members of the forkhead family of transcription factors.[95] FOXO proteins have been implicated in suppression of tumor progression in multiple cancer types.[96–100] Expression of FOXO proteins is negatively correlated with migration, invasion, and metastasis of renal cell carcinoma,[101] lung cancer,[102] prostate cancer,[103] and urothelial cancer.[104] Importantly, FOXO3 inhibits EMT by suppressing activities of β-catenin in prostate cancer[103] and Twist1 in urothelial cancer,[104] while FOXO4 functions as a metastasis-suppressor through counteracting the PI3K/AKT signal pathway in prostate cancer[105] and inhibiting EMT in lung cancer.[106] Although reduced expression of FOXO proteins is correlated with hepatocarcinogenesis and poor survival of HCC patients, direct association of FOXO proteins with HCC metastasis remains unknown.[107–109] MDM2 functions as an E3 ubiquitin ligase for FOXO1, FOXO3, and FOXO4 to promote their degradation.[110–112] However, it remains unsolved whether degradation of FOXO proteins by MDM2 accelerates cancer metastasis.

MDM2 binding protein

MDM2 binding protein (MTBP) was originally identified as a protein that binds to MDM2.[113] Although these two proteins interact exogenously, their endogenous interactions have not yet been demonstrated. Overexpression of MTBP is shown to suppress cell migration and metastasis of osteosarcoma and HCC in alpha-actinin 4 (ACTN4)-dependent and -independent manners.[114–116] Also, in MTBP knockout mice, MTBP

haploinsufficiency increases metastasis of tumors induced in the p53 heterozygous background.[117] Clinically, reduced MTBP expression is associated with reduced patient survival with head and neck carcinoma, as well as capsular/vascular invasion and lymph node metastasis in HCC.[116,118] On the other hand, increased MTBP expression is observed in B-cell lymphoma and triple negative breast cancer where it contributes to tumor progression through its interaction with Myc.[119–121] In another study on human HCC, increased MTBP expression is shown to be associated with increase in MDM2 levels and metastasis, as well as poor survival of HCC patients, which is contrary to previously published studies.[122] Thus, the roles of MTBP in cancer metastasis, the underlying mechanisms, and functional association between MDM2 and MTBP need to be further clarified in the future.

CONCLUSION

Approximately 30% of human cancers have MDM2 overexpression. Specifically, in well differentiated liposarcomas, MDM2 overexpression is detected in over 90% of the cases.[123] These observations indicate significance of MDM2overexpressionincancerprogression. Themechanisms of MDM2 overexpression or hyper-activation include MDM2 gene amplification,[124]single nucleotide polymorphisms in the MDM2 promoter,[125] silencing/ inhibition of MDM2 negative regulators,[126] phosphorylation of MDM2,[127] enhanced translation,[128] or other mechanisms.[129] Although the best characterized function of MDM2 is to inhibit p53 activity, an increasing body of evidence suggests that MDM2 has a p53-independent function. Such function is found specifically when MDM2 is overexpressed. MDM2 mainly exerts its p53-independent function by interacting with its downstream effectors.[11] These effectors frequently play integral roles in cancer progression including cancer metastasis and drug resistance. Indeed, MDM2 overexpression is implicated in cancer metastasis through enhancing EMT, activation/upregulation of other oncoproteins, and suppression of tumor suppressors or metastasis suppressors. However, there is scarce evidence showing direct involvement of MDM2 in invasion and metastasis of HCC. It is thus imperative to have future studies that could appropriately demonstrate the direct role of overexpressed MDM2 in promoting HCC metastasis.

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Table 1

Metastasis promoters interacting with MDM2

Gene	Roles in liver cancer metastasis	Binding to MDM2	Functional association with MDM2	References
HIF-1α	Overexpression of HIF-1α is correlated with vascular invasion and poor survival in human HCC.	Endogenous binding	MDM2 positively regulates HIF-1α expression in MEFs, colon cancer, and osteosarcoma cell lines independent of p53. Conversely, MDM2 is reported to destabilize HIF-1α by promoting its ubiquitination.	[32–39]
Slug	Overexpression of Slug is associated with invasion and metastasis of HCC by repressing E-cadherin.	Endogenous binding	MDM2 stabilizes Slug mRNA in human non-small cell lung carcinoma and colon cancer cell lines.	[41–44]
MMP-9	Overexpression of MMP-9 is well correlated with invasion, metastasis, and poor prognosis in liver cancer.	Unknown	MDM2 increases the MMP-9 promoter activity in breast cancer cell lines.	[46–49,51,52]
HuR/ELAV1	HuR expression is positively correlated with advanced stages in HCC and poor outcomes in HCC patients.	Endogenous binding	MDM2 neddylates HuR, protects it from degradation, and induces its nuclear localization in MEFs, mouse liver progenitor MLP29, colon cancer RKO, and HCC HepG2 cell lines.	[58,60]

HCC: hepatocellular carcinoma; MDM2: murine double minute 2; MEFs: mouse embryonic fibroblasts; HuR: Hu antigen R; HIF-1 α: hypoxia-inducible factor-1-alpha; MMP-9: matrix metalloproteinase 9

Table 2

Metastasis suppressors interacting with MDM2

Gene	Roles in liver cancer metastasis	Binding to MDM2	Functional association with MDM2	References
E-cadherin	Reduced E-cadherin expression is associated with high tumor grade, vascular invasion, intrahepatic metastasis, disease progression, and poor outcomes.	Endogenous binding	MDM2 promotes E-cadherin degradation in breast cancer cell lines.	[68–72]
NME2	NME2 expression is increased in HCC.	Endogenous binding	MDM2 suppresses the ability of NME2 to negatively regulate cell motility in renal cell carcinoma and lung cancer cell lines.	[77–79]
TAp63	Role of TAp63 in HCC metastasis is not explored.	Endogenous binding	MDM2 suppresses TAp63 activity by inhibiting its nuclear localization in MEFs and osteosarcoma cell lines. Conversely, MDM2 increases TAp63 levels and its transcriptional activity in osteosarcoma and monkey kidney fibroblast-like cell lines.	[91,92,94]
FOXO family	Direct association of FOXO proteins with HCC metastasis remains unknown.	Endogenous binding	MDM2 degrades FOXO1, 3, and 4 in MEFs, breast cancer, and lung cancer cell lines.	[110–112]
MTBP	MTBP inhibits HCC migration and metastasis in ACTN4-dependent and -independent manners. Controversially, MTBP may increase HCC metastasis by stabilizing MDM2.	Exogenous	The roles of MTBP in cancer metastasis, the underlying mechanisms, and functional association between MDM2 and MTBP remain to be further investigated.	[114–117,122]

MDM2: murine double minute 2; FOXO: forkhead box O; NME2: non-metastatic cells 2; MTBP: MDM2 binding protein; HCC: hepatocellular carcinoma